includes EDTA (citing Claim 5) and the antibacterial agents include neomycin erythromycin, minocycline, tetracycline, and others in a concentration from 0.5%-10% (citing Col. 9, lines 19-28); and has characterized the Fischetti '299 patent as disclosing that the chelating agents are included in such a way as to synergistically enhance the other components in the formulation (citing Col. 11, lines 30-32). The Examiner has indicated that the Fischetti '299 patent is silent as to the specific synergistic relationship between the chelator, buffer, and antibiotic compounds; but that this relationship is well established, as seen in the Farca study.

The Examiner has newly cited Farca et al. as being a report on the relationship between EDTA-tromethamine complexes and various well-known antibiotic compounds (citing the abstract) and for the disclosure that a synergistic relationship was found for ampicillin and especially oxytetracycline against Gram-positive bacteria such as *Staphylococcus aureus*, *Staphylococcus. hominis* and *Streptococcus faecium* (citing page 2). According to the Examiner, it would have been obvious to apply the concentrations of the Farca study to the formulation of the Fischetti '299 patent in order improve the synergistic bacterial fighting properties of the chelator/buffer/antibiotic combination.

The Examiner has cited the Viegas '443 patent as disclosing a topical wound healing composition comprising chelators such as EDTA (citing Col. 11, lines 18-20), antimicrobial agents such as tetracycline and amikacin (citing Col. 10, lines 20-22), along with buffers such as phosphate and tromethamine (TRIS) which maintain the pH of the formulation at 7.4 (citing Col. 11, lines 35-55). The Examiner indicated that drugs are present in a concentration of the Viegas '443 patent in amounts from 0.1%-60% (citing Col. 11, lines 28-31), while the buffer is present in a concentration of as much as 5%, which is sufficient to maintain the pH at 7.4 (citing Col. 11, lines 50-60), and that the formulation can be applied to wounds as a second skin that delivers active agents to the affected site (citing Col. 5, lines 1-5). The Examiner indicated that "It would have been obvious to include the buffer agents of the '446 patent [*sic*, the Viegas '443

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patent] into the formulation of the '299 patent since they both describe topical wound healing formulations comprising similar chelators, antimicrobial agents, and buffering agents."

Regarding the specific concentration of the chelator compounds, it is the position of the Examiner that such limitation is obviated since the general conditions of the claims have been met by the prior art. It is also the position of the Examiner that the concentration of chelators is merely an optimizable limitation as long as synergy is maintained, and that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation (citing *In re Aller*, 220 F.2d 454 105 USPQ 233, 235 (CCPA 1955).

Finally, it is the Examiner's position that the claims differ from the references by reciting various concentrations of the active ingredient(s). However, the preparation of various compositions having various amounts of the active is within the level of skill of one having ordinary skill in the art at the time of the invention.

This rejection is respectfully traversed.

As previously explained, the Fischetti '299 patent primarily discloses an aerosol composition for treating *Streptococcus pneumoniae, Haemophilus influenzae* or Streptococcus Group A infections of the respiratory tract by delivering the aerosol to the mouth, throat or nasal passage, although passing reference is made to other organisms against which lytic enzymes can be targeted and other delivery routes. The active component of the composition of the Fischetti '299 patent is a lytic enzyme genetically coded by a bacteriophage specific for the specific bacteria of the respiratory tract (or other location) to be treated. The invention of the Fischetti '299 patent is based upon the discovery that phage lytic enzymes specific for bacteria infected with a specific phage can break down the cell wall of the bacterium in question. At the same time, the semipurified enzyme is lacking in proteolytic enzymatic activity and therefore non-destructive to mammalian proteins and tissues when present during the digestion of the bacterial

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cell wall (see Col. 3, lines 6-12). As described in the Fischetti '299 patent, the lytic enzymes are placed in a stabilizing buffer for maintaining the pH of the enzyme composition in a range of about 4.0 to about 9.0. The stabilizing buffer may be a reducing reagent, such as dithiothreitol, a metal chelating reagent, such as ethylenediaminetetraacetic acid disodium salt, or it may contain a phosphate or citrate-phosphate buffer. (See the Fischetti '299 patent, Col. 5, lines 1-12; Col. 6, lines 43-53; and Col. 7, lines 53-64.) Thus, the Fischetti '299 patent appears to disclose the use of amounts (undisclosed) of a chelating agent effective to maintain the pH of the composition in the range of about 4.0 to about 9.0 to stabilize the enzymatic activity of the lytic enzyme. The Fischetti '299 patent contains no disclosure or suggestion of inhibiting proliferation of a bacterial population of a skin injury or surface lesion of a patient by contacting the surface of the skin injury or the surface lesion with an antibacterial composition consisting of from 0.04 wt % to 25 wt % of a pharmaceutically acceptable antibacterial agent, from 0.1 mM to 100.0 mM of a pharmaceutically acceptable chelating agent selected from EDTA, TRIEN and diethyltriamin-pentaacetic acid (DPTA), and an amount of tris (hydroxymethyl) aminomethane effective to maintain the pH of the composition in the range of 7.0 to 9.0 when in contact with the skin injury or surface lesion, wherein the antibacterial agent is present in the composition at a concentration selected to allow synergistic cooperation between the antibacterial agent and the chelating agent, as required by the claims of the present application.

Farca et al. (newly cited) discloses the *in vitro* potentiation of antibacterial effect of some anti-Gram-positive bacterial agents (ampicillin, cephalexin, oxytetracycline, streptomycin and sulphadimethoxine) using dilutions of a solution of 250 mM EDTA and 50 mM tromethane (TRIS), pH 8.0. Farca does not disclose or suggest that the formulations employed could possibly potentiate the antibacterial lytic enzymes of the Fischetti '299 patent, and there would be no motivation for a person skilled in the art to combine the formulations of Farca et al. with the lytic enzyme compositions of the Fischetti '299 patent. In addition, Farca et al. is solely an *in*

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vitro study and does not demonstrate a method of inhibiting proliferation of a bacterial population of a skin injury or surface lesion by contacting the injury or lesion with an antimicrobial composition comprising from 0.04 wt % to 25 wt % of a pharmaceutically acceptable chelating agent selected from EDTA, TRIEN and diethyltriamin-pentaacetic acid (DPTA), an amount of tris (hydroxymethyl) aminomethane effective to maintain the pH of the composition in the range of 7.0 to 9.0 when in contact with the skin injury or surface lesion and a pharmaceutically acceptable carrier, wherein the chelating agent is present in the composition at a concentration in the range of 0.1 mM to 100.0 mM and the antibacterial agent is present in the composition at a concentration selected to allow synergistic cooperation between said antibacterial agent and said chelating agent to inhibit proliferation of the bacterial population of the skin injury or the surface lesion of the human or animal patient, as required by the amended claims. Accordingly, it is submitted that Farca et al. does not overcome the deficiencies of the Fischetti '299 patent, and the present claims would have been nonobvious over Farca et al., either alone or in combination with the Fischetti '299 patent.

The Viegas '443 patent discloses polymer gel formulations for the delivery of drugs or diagnostic agents to the cornea of an eye for use, for example, in connection with laser keratectomy or excimer laser surgery. The formulations of the Viegas '443 patent comprise an aqueous mixture of a film forming, water-soluble polymer and an ionic polysaccharide. The invention of the Viegas '443 patent is based on the discovery that "aqueous pharmaceutical vehicles containing a film forming polymer and an ionic polysaccharide can be gelled and rendered resistant to shear thinning by contacting the mixture with a counter-ion." (See the Viegas '443 patent, Col. 6, lines 9-13.) Especially preferred counter-ion-containing inorganic salts for use as ionic polysaccharide gelling agents include inorganic salts, such as calcium chloride, and are provided in a molar ratio of counter-ion to gellan, chitosan or alginate of about

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1:1 to about 10:1 (see the Viegas '443 patent, Col. 8, lines 34-41). As disclosed in the Viegas '443 patent at Col. 10, lines 7-10:

> The gel compositions formed upon contact with a counter ion for the ionic polysaccharide allow retention of the gel at the desired locus for longer intervals thus increasing the efficiency of action of the delivered drug.

The single appearance of the term "chelating agent" or EDTA in the specification of the Viegas '443 patent occurs at Col. 11, lines 19 and 20, as part of a laundry list of "other drugs" that can be used in the treatment of conditions and lesions of the eyes. However, any EDTA that might potentially be present in a formulation of the Viegas '443 patent would inherently be present for an entirely different purpose than in the antibacterial compositions of the present invention. As disclosed in the present application at page 5, lines 3-7, EDTA is a strong chelating agent that removes divalent cations from the bacterial cell, altering the integrity and permeability of the outer membrane. In accordance with the present claims, the chelating agent and the antibacterial agent are present in the compositions of the claimed methods at a concentration selected to allow synergistic cooperation between said antibacterial agent and said chelating agent to inhibit proliferation of the bacterial population. However, the compositions of the Viegas '443 patent require the presence of high concentrations of a counter ion that would form a counter ion-EDTA coordination complex chelate with any EDTA present, thereby blocking any further chelating function by the EDTA in the composition. Accordingly, the compositions disclosed in the Viegas '443 patent would be inoperable for use in the invention claimed in the present application and teach directly away from the compositions required in the methods of the present claims.

It is readily apparent from the foregoing that the Viegas '443 patent does not overcome the deficiencies of the Fischetti '299 patent and/or Farca et al., and that even when combined, one of ordinary skill in the art could not arrive at the present invention.

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In view of the foregoing comments, it is respectfully submitted that the Examiner has not made out a *prima facie* case of obviousness; that Claims 1, 2, 5-15, 18-22, and 56-62 would not have been obvious under 35 U.S.C. § 103(a) over the combined disclosures of the Fischetti '299 patent in view of Farca et al. and the Viegas '443 patent; and that this rejection of claims should properly be withdrawn.

Double Patenting

The Examiner has further provisionally rejected Claims 1, 2, 5-11, and 56-62 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-3, 14, 15, 18-21, 26-29, 43, and 44 of copending Application No. 10/739,841, and over Claims 1-7, 9-19, 23, 24 and 28-43 of copending Application No. 10/812,668.

Since Application Nos. 10/739,841; 10/812,668; and the current application are subject to rejection(s) on other grounds, this rejection will be addressed when nonstatutory obviousness-type double patenting is the only rejection remaining pursuant to MPEP §804.

CONCLUSION

In view of the foregoing, it is respectfully submit that Claims 1, 2, 5-15, 18-22, and 56-62 are in condition for allowance. Reconsideration and favorable action are requested. The Examiner is further requested to contact applicants' representative at the number set forth below to discuss any issues that may facilitate prosecution of this application.

Respectfully submitted,

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